



# The Development and Utility of a Novel Scale That Quantifies the Glycemic Progression Toward Type 1 Diabetes Over 6 Months

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Jay M. Sosenko,<sup>1</sup> Jay S. Skyler,<sup>1</sup>  
Craig A. Beam,<sup>2</sup> David Boulware,<sup>3</sup>  
Jeffrey L. Mahon,<sup>4</sup> Jeffrey P. Krischer,<sup>3</sup>  
Carla J. Greenbaum,<sup>5</sup> Lisa E. Rafkin,<sup>1</sup>  
Della Matheson,<sup>1</sup> Kevan C. Herold,<sup>6</sup>  
Jerry P. Palmer,<sup>7</sup> and the Type 1 Diabetes  
TrialNet and Diabetes Prevention  
Trial–Type 1 Study Groups\*

## OBJECTIVE

We developed a scale to serve as a potential end point for 6-month glycemic progression (PS6M) toward type 1 diabetes (T1D) in autoantibody-positive relatives of individuals with T1D.

## RESEARCH DESIGN AND METHODS

The PS6M was developed from Diabetes Prevention Trial–Type 1 (DPT-1) data and tested in the TrialNet Pathway to Prevention Study (PTP). It is the difference between 6-month glucose sum values (30–120 min oral glucose tolerance test values) and values predicted for nonprogressors.

## RESULTS

The PS6M predicted T1D in the PTP ( $P < 0.001$ ). The area under the receiver operating characteristic curve was greater ( $P < 0.001$ ) for the PS6M than for the baseline-to-6-month difference. PS6M values were higher in those with two or more autoantibodies, 30–0 min C-peptide values  $<2.00$  ng/mL, or DPT-1 Risk Scores  $>7.00$  ( $P < 0.001$  for all).

## CONCLUSIONS

The PS6M is an indicator of short-term glycemic progression to T1D that could be a useful tool for assessing preventive treatments and biomarkers.

The end point of a diagnosis of type 1 diabetes (T1D) in prevention trials necessitates monitoring many autoantibody-positive subjects for years (1–3). Because that end point limits the number of potential treatments for study, alternative end points are needed that would facilitate the performance of shorter trials with fewer subjects. Importantly, such alternative end points could also facilitate the evaluation of potential biomarkers for T1D.

We have observed that glucose levels tend to gradually increase for several years before the diagnosis of T1D (4–6) in autoantibody-positive individuals. This information led us to examine whether changes in glucose levels during a 6-month period could be used to formulate a progression scale to expedite assessments of potential T1D preventive treatments and biomarkers.

## RESEARCH DESIGN AND METHODS

### Subjects

The Diabetes Prevention Trial–Type 1 (DPT-1) and the TrialNet Pathway to Prevention Study (PTP) have been described in detail (1,2,7). All participants were

<sup>1</sup>Division of Endocrinology, University of Miami, Miami, FL

<sup>2</sup>Division of Epidemiology and Biostatistics, University of Western Michigan School of Medicine, Kalamazoo, MI

<sup>3</sup>Division of Informatics and Biostatistics, University of South Florida, Tampa, FL

<sup>4</sup>Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada

<sup>5</sup>Benaroya Research Institute at Virginia Mason, Seattle, WA

<sup>6</sup>Department of Immunobiology, Yale University School of Medicine, New Haven, CT

<sup>7</sup>VA Puget Sound Health Care System; Division of Endocrinology, Metabolism, and Nutrition, University of Washington, Seattle, WA

Corresponding author: Jay M. Sosenko, jsosenko@med.miami.edu.

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pancreatic autoantibody-positive relatives of patients with T1D. Those included in the analysis underwent a 2-h oral glucose tolerance test (OGTT) at baseline and within  $6 \pm 3$  months from the baseline OGTT. Individuals diagnosed with T1D at or before the 6-month OGTT were excluded from the analysis. Both studies were approved by institutional review boards at all participating sites, and written informed consent or assent, as appropriate, was obtained in both studies.

### Procedures

DPT-1 and PTP participants underwent 2-h OGTT surveillance at intervals of  $6 \pm 3$  months. OGTTs were repeated for the diagnostic confirmation of T1D when fasting glucose values were  $\geq 126$  mg/dL and/or 2-h glucose values were  $\geq 200$  mg/dL if individuals were asymptomatic. Plasma glucose levels were measured by the glucose oxidase method. C-peptide was measured with the Tosoh assay (8).

### Data Analysis

We have developed and tested a scale of glycemic progression to T1D by 1) characterizing the glycemic progression of DPT-1 nonprogressors, 2) using this as a basis for a scale measuring glycemic progression relative to that expected for nonprogressors, and 3) obtaining another scale based on PTP nonprogressors with the same method. These two scales were subsequently compared within the full PTP population of progressors and nonprogressors. The details are presented below.

Among nonprogressors to T1D followed for over 2 years after the 6-month visit in DPT-1 (median: 3.98 years; 25th percentile: 3.03 years; 75th percentile: 4.89 years), a linear regression equation was obtained for the association of the glucose sum (sum of glucose values at 30, 60, 90, and 120 min) at 6 months with the glucose sum at baseline. (Baseline and 6-month mean  $\pm$  SD glucose sum values are reported in Supplementary Table 1.) The equation describing the association ( $r = 0.59$ ;  $n = 245$ ) was:

$$\begin{aligned} \text{predicted 6-month glucose sum for DPT-1} \\ \text{nonprogressors} = 204 + 0.599 \\ \times \text{glucose sum at baseline} \end{aligned}$$

There was no significant difference in the regression curves between those aged  $<13.0$  years ( $n = 124$ ) and those aged  $\geq 13.0$  years ( $n = 121$ ).

That DPT-1 equation for nonprogressors was then used to develop a progression scale for 6 months (PS6M), as described by the following equation:

$$\begin{aligned} \text{PS6M} = \text{actual glucose sum at 6 months} \\ - (204 + 0.599 \times \text{glucose sum at} \\ \text{baseline for nonprogressors}) \end{aligned}$$

To assess whether the PS6M from DPT-1 could be used in other autoantibody-positive populations, we obtained a second linear regression equation ( $r = 0.61$ ;  $n = 397$ ) for the 6-month glucose sum of PTP nonprogressors:

$$\begin{aligned} \text{predicted 6-month glucose sum for PTP} \\ \text{nonprogressors} = 187 + 0.632 \\ \times \text{glucose sum at baseline} \end{aligned}$$

The PS6M<sub>PTP</sub> is described by the following equation:

$$\begin{aligned} \text{PS6M}_{\text{PTP}} = \text{actual glucose sum at 6 months} \\ - (187 + 0.632 \times \text{glucose sum} \\ \text{at baseline for nonprogressors}) \end{aligned}$$

The  $t$  test was used for comparisons between groups. Proportional hazards regression and Kaplan-Meier estimations were used to assess the occurrence of T1D. Areas under receiver operating characteristic curves were also calculated. SAS 9.1.3 and 9.2 software was used for the analysis. Confidence intervals and  $P$  values are two-sided, except for sample size estimations, which use one-sided  $P$  values; TrialNet protocols are performed on the basis of one-sided  $P$  values.

## RESULTS

The analysis included 1,245 PTP participants (mean  $\pm$  SD age:  $18.2 \pm 13.2$  years; 47% male) with baseline and 6-month OGTTs.

### Applicability of PS6M for PTP Participants

The equation shown below describes the relationship in the full PTP cohort (progressors and nonprogressors) between progression scale values based on PTP nonprogressors (PS6M<sub>PTP</sub>) and on DPT-1 nonprogressors (PS6M).

$$\text{PS6M}_{\text{PTP}} = -0.011 + 0.993 \times \text{PS6M}$$

The equation and the accompanying scatterplot (Supplementary Fig. 1) show that PS6M and PS6M<sub>PTP</sub> values were almost identical; the regression line

essentially crossed the 0 mg/dL value. We used the PS6M in the analyses shown below for the PTP cohort because its development was independent of that cohort.

### Prediction of T1D

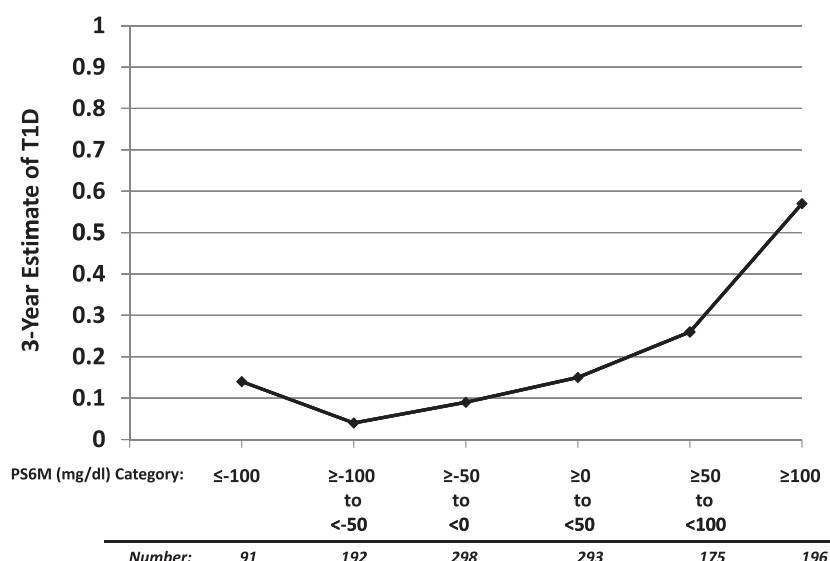
The PS6M was a strong predictor of T1D among PTP participants. Proportional hazards regression showed a substantial overall association of the subsequent development of T1D with PS6M values ( $\chi^2 = 178$ ;  $P < 0.001$ ). The fourth quartile-to-first quartile hazard ratio (with 95% CIs) for T1D of the PS6M (7.12 [4.32, 11.72];  $P < 0.001$ ) was much greater ( $P < 0.001$ ) than the fourth quartile-to-first quartile hazard ratio for T1D of the baseline-to-6-month difference (1.40 [1.22, 1.60];  $P < 0.001$ ). The area under the receiver operating characteristic curve (Supplementary Fig. 2) was also substantially greater ( $P < 0.001$ ) for the PS6M (0.75 [0.71, 0.79];  $P < 0.001$ ) than for the baseline-to-6-month difference (0.64 [0.60, 0.69];  $P < 0.001$ ). The association of T1D with the PS6M was nonlinear (Fig. 1). The 3-year risk remained low for PS6M values  $<0$  mg/dL and then increased appreciably, such that the 3-year risk exceeded 0.50 for PS6M values  $\geq 100$  mg/dL.

### Assessment of Associations With Biomarkers

The PS6M was used to assess associations of 6-month glycemic progression with known T1D biomarkers. PS6M values were greater in PTP participants with two or more autoantibodies at baseline than in those with one autoantibody ( $28 \pm 102$  mg/dL [ $n = 570$ ] vs.  $6 \pm 84$  mg/dL [ $n = 675$ ];  $P < 0.001$ ). PS6M values were also greater in participants with baseline 30–0 min C-peptide values  $<2.00$  ng/mL than with values  $\geq 2.00$  ng/mL ( $43 \pm 98$  mg/dL [ $n = 214$ ] vs.  $11 \pm 91$  mg/dL [ $n = 1,027$ ];  $P < 0.001$ ), and in participants with baseline DPT-1 Risk Score (9) values  $>7.00$  than with values  $\leq 7.00$  ( $56 \pm 119$  mg/dL [ $n = 256$ ] vs.  $6 \pm 82$  mg/dL [ $n = 989$ ];  $P < 0.001$ ).

### Potential Use in Short-term Prevention Trials

With PS6M as an end point, a controlled trial of individuals with two or more autoantibodies (equal numbers, one-sided  $P$  values with a significance of  $P < 0.05$  and a power of 0.80 for a 50% reduction of those exceeding a PS6M threshold) could be performed with as few as 46 participants per group. Alternatively,



**Figure 1**—Three-year risk estimates are shown according to PS6M categories. The 3-year risk estimates are low until PS6M values are above zero and then increase substantially with increasing PS6M values.

uncontrolled pilot studies can be performed. For example, to test (power = 0.80, one-sided  $P$  value = 0.05) whether a potential treatment can lower the PS6M from a previously observed mean value of 30 mg/dL in a particular target population to the expected mean value for nonprogressors (i.e., 0 mg/dL), as few as 43 subjects (all on treatment) would be needed.

## CONCLUSIONS

The applicability of the PS6M across autoantibody-positive populations, its prediction of T1D, and its associations with T1D biomarkers suggest that the PS6M can help to facilitate the evaluation of preventive treatments and biomarkers of T1D. The PS6M is uniquely suited for these purposes because it is indicative of the change in glycemia over a short, specified period of time. It was a far better predictor of T1D than the difference in glucose values between the OGTTs. The PS6M acts as a frame of reference for progression toward T1D because it is based on the expected 6-month glucose sum values of nonprogressors.

The PS6M could reduce numbers and the length of follow-up, and thus increase the feasibility for assessing multiple potential preventive treatments in early-phase clinical trials. It is conducive for performing uncontrolled pilot studies because the reduction of PS6M values toward the expected average value for nonprogressors (i.e., 0 mg/dL) could serve as an end point. Although highly predictive, the PS6M is not a diagnostic

surrogate for T1D per se. Rather, it would indicate the effect of an intervention on the glycemic progression toward T1D.

The higher PS6M values among those with multiple autoantibodies, low 30–0 min C-peptide values, or high DPT-1 Risk Score values indicate that the PS6M can also be used to assess the influence of biomarkers upon short-term changes in glycemia. As new biomarkers are discovered, there is a need to examine how they relate to changes in glycemia during the progression to T1D.

Because the PS6M was developed in autoantibody-positive relatives of patients with T1D, its use should be restricted to those populations. Moreover, although the PS6M was developed in DPT-1 and tested in the PTP, its applicability in other autoantibody-positive populations is not a certainty.

There are no prior reports of changes in glycemia during a 6-month period for use as an end point. Changes in HbA<sub>1c</sub> and C-peptide during a 2-year period have previously been assessed as possible end points (10).

In conclusion, as an indicator of short-term glycemic progression toward T1D, the PS6M provides a potentially useful tool for assessing preventive treatments and biomarkers of T1D.

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